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Maternal Health Memorandum

Date: April 7, 2016 **Date consulted:** October 25, 2016

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To: Division of Non-Prescription Drug Products (DNDP)

Drug: acetaminophen

TSI: 1355

Subject: Recent findings associating acetaminophen use in pregnancy with attention deficit/hyperactivity disorder (ADHD).

Materials Reviewed:

- DPMH Consult Request Form with associated attachments:
  - OSE/DEPI reviews of the published literature
    - By A. Mosholder, MD, MPH, dated October 14, 2016 (DARRTS Ref ID 3999031, RCM 2016-1871) and March 18, 2015 (DARRTS Ref ID 3884226, RCM 2015-387)
    - By L. Taylor, PhD, dated May 15, 2014 (DARRTS Ref ID 3507534, RCM 2014-689)
  - Clinical TSI Integrated Review Memorandum, by V. Pratt, MD, dated March 9, 2016 (DARRTS Ref ID 3899199)
  - "Prescription and Overt-the-Counter (OTC) Pain Medicines: Drug Safety Communication – FDA Review of Possible Risks of Pain Medicine Use During Pregnancy", posted January 9, 2015

Reference ID: 4081673

Consult Question:

> **"**The 2016 DEPI review describes four recent publications – two provide modest evidence in favor of an association between prenatal acetaminophen exposure and behavioral/attentional problems and two articles provide weak evidence for an association between acetaminophen use and effects on IQ or motor delay. Recognizing the limitations of these studies, the different outcomes measured, potential confounders during pregnancy (e.g., maternal fever), and the known adverse effects associated with the use of other analgesics during pregnancy (e.g., NSAIDs, opioids), DNDP requests DPMH comment on the clinical relevance of the acetaminophen findings and opine on whether further public communication about this safety issue is warranted."

PURPOSE

The purpose of the memorandum is to provide advice to the Division of Non-Prescription Drug Products (DNDP) to address questions on clinical relevance and need for further Drug Safety Communication regarding use of acetaminophen use during pregnancy and a potential association with attention deficit/hyperactivity disorder (ADHD).

REGULATORY HISTORY

- February 2014, article by Liew Z *et al.,* in JAMA Pediatrics reported an increased association between APAP use in pregnancy and attention deficit/hyperactivity disorder (ADHD) in the offspring.[1]
- May 15, 2014, TSI 1355 opened for acetaminophen (APAP) and effects during pregnancy
- May 15, 2014, Division of Epidemiology (DEPI) review concluded, "The study's findings are difficult to interpret due to methodologic limitations and in the context of other existing data." DEPI recommended no regulatory action be taken at that time and continued vigilance.
- September 2014, an article by Thompson J *et al.,* in PLOS One reported an association between acetaminophen use during pregnancy and ADHD symptoms.[2]
- January 9, 2015, the Agency issued Drug Safety Communication (DSC), *Prescription and Over-the-Counter (OTC) Pain Medicines: Drug Safety Communication – FDA Review of Possible Risks of Pain Medicine Use during Pregnancy*. The DSC stated that data are "too limited to make any recommendations" at this time, and it encouraged healthcare professionals talk with each patient about the benefits and risk of analgesic use during pregnancy, which may differ among patients and by treatment indication.
- March 18, 2015, DEPI I completed a second review concluding that "whether the association in causal in nature is still uncertain" and "preclinical data may be more informative in that regard."

[1] Liew Z et al. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. JAMA Pediatr 2014;168(4):313-320.

[2] Thompson J et al. Associations between acetaminophen use during pregnancy and ADHD symptoms measured at ages 7 and 11 years. PLOS One 2014;9(9):e108210.

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- February 8, 2016, Pharmacology/Toxicology consultation review concluded, "The available nonclinical data…do not describe studies in animals that were adequately designed and conducted to address the question posed by OSE…at this time, the behavioral responses in animals that are most likely predictive of an ADHD response in humans are uncertain and, therefore, additional animal studies are not likely to be informative".
- March 1, 2016, DNDP, DEPI I, and Nonclinical met to discuss the available data and agreed that the data do not support a causal association between acetaminophen and ADHD at this time. The January 9, 2015 DSC adequately informed the public of this issue. It was agreed that TSI 1355 should be closed
- October 14, 2016, DEPI I reviewed the four recent articles published in summer 2016. Further details provided below.

BACKGROUND

Acetaminophen Use in Pregnancy

Acetaminophen is the over-the-counter (OTC) drug of choice (compared to NSAIDs) and generally considered to safe to use for short-term pain relief and reduction of fever during all trimesters of pregnancy.[3] Often found in combination products and prescription pain medications, care must be taken to avoid acetaminophen overuse and the drug's potential toxicity to the liver and kidneys. Chronic use and/or high daily doses of acetaminophen during pregnancy can lead to maternal morbidity and fetal/neonatal mortality.[4]

Prior DPMH Reviews

There is a long history of acetaminophen use in pregnancy. Several published observational studies have evaluated the potential association between acetaminophen and adverse pregnancy-related outcomes. DPMH reviewed the published literature in 2010, and again in 2015, subsequent to the January 2015 DSC, in relation to acetaminophen injection.[5,6] Conclusions of the reviews found no increase in overall major congenital malformations associated with use of acetaminophen during pregnancy when compared to the background rate in the general population, and inconsistent data regarding the presence or absence of any one specific malformation.

Data regarding a possible association of *in utero* acetaminophen exposure and the risk of developing persistent childhood wheezing and asthma were also reviewed. Limitations of the study design, confounders, and inconsistent study results precluded a clear determination of causality; however, additional investigation of this potential safety signal was warranted.

[3] Your Pregnancy and Childbirth: Month to Month. Sixth Edition. (2015) Washington, DC: The American College of Obstetricians and Gynecologists.
[4] Gerald G. Briggs, Roger K. Freeman, Sumner J. Yaffe. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk — Tenth edition. (2015) Philadelphia, PA: Wolters Kluwer Health.
[5] Pediatric and Maternal Health Staff review, NDA 22450, by L. Sahin, dated February 9, 2010.
[6] Division of Pediatric and Maternal Health review, NDA 206610, by L. Sahin, dated February 9, 2015.

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REVIEW

Summary of Division of Epidemiology Review

DEPI I has reviewed the recent additional four articles published in summer 2016 and the three publications cited in the DSC. With the addition of the study published by Thompson et al. 2014, DEPI I found that the eight observational studies varied in quality, with seven showing some association with adverse neurodevelopmental outcomes (i.e., ADHD behavioral symptoms, lower IQ, and delayed developmental milestones). The study by Streissguth et al. 1987 was negative for the association. (See the Appendix for DEPI's summary of the outcomes from the published observational study results[7].) The studies had some limitations in common that hinder clearer determination of causality:

- Lack of details on dose and duration of APAP use in mothers
- No pattern of exposure that suggests a critical gestational age for the outcome
- Confounding by maternal fever or infection

DEPI concludes that *in utero* APAP exposure is associated with adverse neurodevelopmental outcomes as demonstrated reproducibly across the seven studies; nonetheless, a causal relationship has not been established. DEPI recommends Agency communication to consumers and healthcare providers to reflect:

1. Current data raise the possibility of neurodevelopmental harm to the fetus from maternal APAP use (even without proof of a causal relationship), and APAP should be used judiciously during pregnancy,
2. Other analgesics are associated with more definite pregnancy risks, and
3. APAP may be needed as an antipyretic to reduce risks associated with maternal fever.

Reviewer Comment

Using the term "adverse neurodevelopmental outcomes" broadens the scope of these potential associations unnecessarily. The studies demonstrate some consistency of association among the outcomes related to attention problems and general behavioral problems; however, the risk estimates for the reported outcomes in the studies are less than two times greater among the exposed group than the unexposed group. The difficulty is that these studies may only be demonstrating a common finding due to common use of the drug in the pregnant population, and are not sufficient to establish a specific drug-associated risk. Furthermore, the outcomes of lower IQ and delayed motor development are inconsistent and their inclusion under the term "adverse neurodevelopmental outcomes" is not supported. Therefore, any Agency communication should re-iterate the prior DSC messaging regarding ADHD and should be clear regarding the specific related outcomes to avoid misinterpretation of the available clinical information.

Other Resources for Clinical Information

- The ReproTox database reports on the same key articles reviewed by DEPI, however, topline conclusion states that APAP use in pregnancy "does not appear to increase the risk of adverse outcomes".
- The TERIS database has not been updated to reflect the recent 2016 publications, and only refers to the results of the Liew *et al.* 2014 article for an association with ADHD.

[7] OSE/DEPI review, by A. Mosholder, MD, MPH, dated October 14, 2016 (DARRTS Ref ID 3999031).

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TERIS stated there is minimal risk for both neurodevelopmental abnormalities and congenital anomalies with usual therapeutic doses of acetaminophen.

- The UpToDate peer-review database briefly reflects upon published literature regarding epidemiologic studies reporting an association between *in utero* APAP exposure and the risk of attention-deficit/hyperactivity disorder-like behaviors. The database cited methodological limitations of the literature (i.e., lack of assessment of overall health for the index pregnancy, lack of information on acetaminophen strength and dosage taken, and lack of assessment of attention-deficit/hyperactivity disorder).[8]

DISCUSSION/ RECOMMENDATIONS

The findings of the clinical studies demonstrate some consistency of association among the outcomes related to attention problems and general behavioral problems; however, the studies may only be demonstrating a common finding due to common use of the drug in the pregnant population.

DPMH agrees that some communication is needed to meet the public's expectation of the Agency's assessment of press in August 2016 that we are actively reviewing the new information. The communication would update the data review, while maintaining a balance with the benefits of acetaminophen use. Because there are no alternative OTC medications to manage pain and/or fever during pregnancy, to raise concerns of a strengthened association with "adverse neurodevelopmental outcomes", when important limitations exist for the data and no causal relationship can be established, would have a significant public health impact for the pregnant population and their healthcare providers. An update to the DSC may address immediate inquiries about the recent publications, but care must be taken to avoid invoking more concern than warranted at this time and unintentional repercussions (e.g., no treatment of maternal fever) on pregnant patients and their healthcare providers. Note that the current DSC already communicates the key message and the advice to the public does not change substantially from the January 2015 DSC:

> Pregnant women should always consult with their health care professional before taking any prescription or OTC medicine. Women taking pain medicines who are considering becoming pregnant should also consult with their health care professionals to discuss the risks and benefits of pain medicine use. Health care professionals should continue to follow the recommendations in the drug labels when prescribing pain medicines to pregnant patients. We will continue to monitor and evaluate the use of pain medicines during pregnancy and will update the public as new safety information becomes available.

[8] Lockwood CJ, Magriples U. Initial prenatal assessment and first-trimester prenatal care. UpToDate, accessed January 6, 2017.

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APPENDIX
DEPI's Summary of the Outcomes from the Published Observational Study Results[9]

Cognitive development

Study	Outcome	Finding for prenatal APAP exposure versus unexposed
Avella-Garcia 2016	IQ	No significant association
Liew 2016	IQ	Mean -3.4 points in absence of maternal fever
Streissguth 1987	IQ	No significant association (aspirin associated with lower IQ)

→Mean -4.3 points with fever and no APAP use

Attention problems

Study	Outcome	Finding for prenatal APAP exposure versus unexposed
Avella-Garcia 2016	ADHD symptoms	Increased risk
	Continuous performance task	Increased errors
Liew 2014	Diagnosis of Hyperkinetic Disorder	Increased risk (HR 1.4, 95% CI 1.2-1.6)
	Use of ADHD drugs	Increased risk (HR 1.3, 95% CI 1.2-1.4)

[9] From OSE/DEPI review, by A. Mosholder, MD, MPH, dated October 14, 2016 (DARRTS Ref ID 3999031)

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Stergiakouli 2016	SDQ hyperactivity score 7+	Increased risk (HR 1.2, 95% CI 1.0-1.4)
Streissguth 1987	Video vigilance task	No association (aspirin exposure associated with more errors)
Thompson 2014	Conners scale	Elevated subscales, but not elevated overall ADHD index

Motor development

Study	Outcome	Finding for prenatal APAP exposure versus unexposed
Avella-Garcia 2016	Bayley aged 15 mos. and McCarthy aged 5 yrs.	No associations
Brandlistuen 2013	Motor milestones age 3	Significantly more psychomotor problems
Vlenterie 2016	Walking at 18 months	Delayed

Autistic behaviors

Study	Outcome	Finding for prenatal APAP exposure versus unexposed
Avella-Garcia 2016	Childhood Autism Spectrum Test	In males, dose-related increase in reported autistic signs/symptoms; in females fewer symptoms
Zerbo 2013	Case-control study of autistic spectrum disorders	Maternal fever associated with autistic spectrum disorders, antipyretic use attenuated association

General behavioral problems

Study	Outcome	Finding for prenatal APAP exposure versus unexposed
Brandlistuen 2013	Child Behavior Checklist age 3	Increased behavior problems
Liew 2014	Strengths and Difficulties Questionnaire age 7	Increased risk of high "Total Difficulties" score
Stergiakouli 2016	Strengths and Difficulties Questionnaire age 7	Increased risk of high "Total Difficulties" score (later pregnancy exposure)
Thompson 2014	Strengths and Difficulties Questionnaire ages 7, 11	Increased scores

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/s/

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